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Abstract

The mechanisms that control cell fate behaviour during development, and the factors leading to their dysregulation in disease, remain the subject of interest and debate. Lately, advances in single-cell genomics have shifted emphasis towards the elucidation of molecular regulatory programmes and transcriptional cell states. However, quantitative statistical approaches based on cell lineage tracing data have provided fresh insight into stem and progenitor cell behaviour, questioning the role of cell fate stochasticity, transcriptional heterogeneity and state priming. These investigations, which draw upon conceptual insights from statistical physics and mathematics, provide a novel, generic and rigorous framework to resolve and classify stem cell self-renewal strategies, which heavily constrain, but do not seek to define, underlying molecular mechanistic programmes. Here, using epithelial maintenance as an exemplar, we consider the foundation, conceptual basis, utility and limitations of such quantitative approaches in cell biology.

Keywords	Universality; Scaling; Cell fate regulation; Lineage tracing; Epidermis

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Highlights

- Collective dynamics of molecules or cells can give rise to “emergent” quantities
- Methods from statistical physics allow identifying these degrees of freedom
- Scaling and universality are useful concepts to study cell fate regulation
- These concepts are exemplified in the context of clone dynamics in mouse epidermis

Emergence and universality in the regulation of stem cell fate

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Abstract:
The mechanisms that control cell fate behaviour during development, and the factors leading to their dysregulation in disease, remain the subject of interest and debate. Lately, advances in single-cell genomics have shifted emphasis towards the elucidation of molecular regulatory programmes and transcriptional cell states. However, quantitative statistical approaches based on cell lineage tracing data have provided fresh insight into stem and progenitor cell behaviour, questioning the role of cell fate stochasticity, transcriptional heterogeneity and state priming. These investigations, which draw upon conceptual insights from statistical physics and mathematics, provide a novel, generic and rigorous framework to resolve and classify stem cell self-renewal strategies, which heavily constrain, but do not seek to define, underlying molecular mechanistic programmes. Here, using epithelial maintenance as an exemplar, we consider the foundation, conceptual basis, utility and limitations of such quantitative approaches in cell biology.

Main text

The development and maintenance of multicellular organisms rely on the integration of control mechanisms that span a wide range of scales: Cellular function arises from the complex network interactions between genes and gene products, while gene expression is influenced both by cell-intrinsic factors -transcriptional and epigenetic programs- and extrinsic influences through signalling pathways, chemical gradients and mechanical cues. In turn, the development and function of tissues arise from the interplay of cellular interactions, cell movements and collective fate decisions. Understanding how molecular components interact to coordinate function at the cellular and tissue scale remains a formidable challenge (*1–3*).

Advances in single-cell profiling methods afford unprecedented access to transcriptional and epigenetic states (*4*), provoking renewed interest in the definition of molecular identity (*5*). Implicit in the excitement is the notion that the integrated computational analysis of single-cell data will provide the basis to develop predictive mechanistic insights into the regulation of cellular processes and function (*6*, *7*). But how can quantitative information at the molecular scale be translated into biological function at the cellular and tissue scale? To frame this question, it is interesting to reflect on how lessons from the physical sciences might inform on a conceptual framework to address complexity in biological systems.

In the realm of "low-energy" physics, the basic building blocks of nature and their interactions were defined almost a century ago. As articulated (mischievously) by Robert Laughlin during his Nobel lecture, in the terrestrial world, physical scientists have the "Theory of Everything" (*11*). Matter is made up of electrons and ions, and these particles interact through electromagnetic forces. By fixing stoichiometry and temperature, the "fundamental theory" –encapsulated in the quantum mechanical Schrodinger equation– can describe everything; air, water, rocks, etc…! After a moment of reflection, it quickly becomes evident that such a fundamental theory isn't a *practical* theory of anything. To quote Philip Anderson (*10*), "…the reductionist hypothesis does not… imply a 'constructionist' one: The ability to reduce everything to simple fundamental laws does not imply the ability to start from those laws and reconstruct the universe." In his influential essay, "More is Different", written almost 50 years ago, Anderson goes on to say, "The constructionist hypothesis breaks down when confronted with the twin difficulties of scale and complexity. The behavior of large and complex aggregates of elementary particles, it turns out, is not to be understood in terms of a simple extrapolation of the properties of a few particles. Instead, at each level of complexity entirely new properties appear…"

Although now somewhat clichéd, these insights seem particularly prescient as biology enters an era in which the "fundamental building blocks" –the genes are gene products- and their interactions are becoming resolved. The triumph of 19th and 20th century physics was to understand that complexities at the microscopic –or nano– scale translate to (often unexpected) *emergent* phenomena at the mesoscale that cannot be predicted, or even conceived, from the behaviour of two or three "elemental" particles (*10*, *11*). For example, when tuned by pressure or temperature, interactions between atoms or molecules in a liquid can drive a transition into an ordered crystalline phase in which fundamentally new collective excitations –sound waves– emerge. Similarly, when electrons or atoms condense into the same quantum state, there emerge new collective phenomena in the form of a "super-flow" involving the dissipationless transport of current. Importantly, these emergent behaviours are often encapsulated through "coarse-grained", or *hydrodynamic*, theories involving few composite variables, themselves complex and usually unknown functions of the fundamental or microscopic parameters. But why should it be that details at a microscopic scale can be surrendered without losing information on the dynamics at the macroscale?

Crucially, when systems are poised at the transition point between phases, statistical fluctuations can become length-scale independent. In such *critical* states, hydrodynamic theories can be systematically derived by successive coarse-graining of the microscopic

degrees of freedom, a process known as “renormalization” (*12*) in which, at the largest scales, the properties of different microscopic models converge or “flow” to those of the same hydrodynamic theory. In this way, the phase behaviour of entirely different physical systems, such as magnets or liquids, obtain equivalent statistical dependences defined by the same theory. In the language of statistical physics such “attractor theories” constitute *universality classes*.

In physics, much of the focus has been on the equilibrium –or near-equilibrium– phase behaviour of (often complex) ensembles of inanimate particles or compounds. These days, the question of whether and how collective phenomena emerge in driven non-equilibrium systems has evolved as a major frontier of statistical physics (*13*), embracing phenomena such as jamming in particulate matter (*14*), swarming and flocking of active systems (*15*, *16*), epidemics (*17*), voting patterns (*18*), risk management and financial markets (*19*), to mention just a few. In many such cases, it has been found empirically that systems positioned far from equilibrium may be driven towards critical states by collective dynamics, even without fine-tuning of parameters. Therefore, as in critical equilibrium states, the large-scale statistical properties non-equilibrium systems are defined by a limited number of “universal” theories obtained as the renormalization “fixed points” of whole classes of distinct microscopic models (Fig. 1). Under these conditions, probability distributions of critical states often converge to self-similar “scaling” forms at long times, such that their behaviour is entirely defined by a single, time-dependent scale. Can such concepts of emergence and universality provide insight into the behaviour of living systems, where the constant flux of energy from the environment leaves them far from thermal equilibrium? In the following, we will consider how emergence and universality can provide insight into cell fate decision making in mammalian tissues.

In adult, cycling tissues such as the skin epidermis, blood and the intestinal epithelium are maintained by sub-populations of proliferative cells known as stem cells (*20*). To achieve homeostasis, these cells must perfectly balance proliferation and differentiation, to replenish functional differentiated cells lost through migration or exhaustion (*21*, *22*). For any given tissue, individual stem cell fate decisions are influenced by multiple factors arising from both cell-intrinsic programs and external cues from neighboring cells, extracellular matrix proteins and chemical signaling gradients that together constitute the stem cell niche(*23*). Yet, to define the long-term fate behavior of stem cells, are all these inputs and variables *always* important? While the fate outcome of an individual stem cell division may be unpredictable, conditional on variable spatial and temporal cues, the dynamics of an ensemble of stem cells may conform to “simple” and rigorous statistical “rules” that find a signature in emergent long-term behavior.

To understand how such collective behavior can emerge, and what insight it can offer, the maintenance of mouse epithelia is paradigmatic. In mouse, the skin epidermis is comprised of hair follicles and sebaceous glands interspersed with interfollicular epidermis (IFE) (*24*). The IFE forms a stratified two-dimensional epithelium, with proliferation restricted to the basal layer (Fig. 2A). The esophagus shows a similar organization but lacks appendages (*25*). As cells commit to differentiation, they detach from the basement membrane, mature and migrate through the suprabasal layers, eventually becoming shed from the surface of the skin. How do proliferative basal cells function to maintain the lifelong turnover of tissue?

To trace the fate behavior of stem cell and their progeny, emphasis has been placed on cell lineage tracing assays based on intravital imaging (*26*) or genetic labelling using transgenic animal models (*27*). Through the controlled activation of a fluorescent reporter gene in targeted subpopulations of cells, the fate of individual marked cells and their progeny – termed clones– can be traced over a defined time course (Fig. 2B) (*28*). Applied to mouse tail IFE and esophagus, early studies based on unbiased labelling revealed unexpectedly heterogeneous and evolving clone size distributions, with some clones bearing only a handful of cells after months of tracing while others span tens or even hundreds of cells (Fig. 2C) (*25*, *29*). Yet, analysis of clone density shows that the increase in the average size of surviving clones is perfectly compensated by continuous clonal loss so that the overall labelled cell number remains approximately constant in size over time – a signature of homeostatic tissue turnover (Fig 2C). Altogether, these results indicate that basal progenitors follow variable fate decisions so that some clones become lost through chance differentiation while others expand to maintain tissue.

But what is the origin of such cell fate heterogeneity? In the structured environment of mouse epidermis, variability might be expected to emerge from a combination of factors, ranging from transcriptional noise driving fate priming, to regional variations associated with dermal factors and skin appendages. However, notably, despite the increase in the average clone size, quantitative analysis of the size distribution shows that, after a transient period, the chance of finding a clone larger than some multiple of the average size becomes constant over time (Fig. 2E), the *emergent* property of scaling (*21*, *29*, *30*). This empirical observation is both intuitive and important.

First, by showing that the distribution of clone sizes adopts a scaling form, it follows that the cell fate behaviour of the tissue-maintaining population is stochastic with fate probabilities that are fixed and encoded in the average clone size dependence (*21*, *30*). Second, from the scale invariance of the clone size distribution, it follows that the tissue-maintaining progenitor population must function long-term as a single pool of statistically equivalent cells (*29*). Such behaviour does not preclude the potential for short-term fate priming towards proliferation or differentiation; it simply means that, if it exists, such bias must become resolved over time.

But how does scaling behaviour arise and how can it offer mechanistic insights? To address this question, it is helpful to consider the constraints that act on the tissue-maintaining population. To achieve homeostasis, cell duplication by division must, on average, be compensated by cell differentiation and loss (stratification out of the basal cell layer in this case) (Fig. 2C). Under these conditions, clone dynamics can be shown rigorously to converge towards a critical state, where the long term statistical properties of the clone size distribution become indistinguishable from that of a simple theory involving only cell loss and replacement within a single compartment -a model introduced historically to study patterns of voting behaviour. More formally, in the long-term, statistical fluctuations of clone size are controlled by an attractor of the renormalisation flow, leading to stereotypic behaviour of the size distribution(*31*). In the case of homeostatic clone dynamics, this attractor defines the *voter model universality class*, in which the size distribution depends only on spatial dimension, i.e. the spatial coordination of cells (Fig. 1C). In the vernacular of

non-equilibrium statistical physics, the development of statistical scaling behaviour of clone sizes is a “robust” emergent phenomenon. All underlying cellular mechanisms of tissue homeostasis, however intricate and complex, must fall into one of these classes.

In the case of mouse epidermis, balance between stem cell loss and replacement could be enforced through cell-autonomous regulation where, for example, the stochastic expression of cell fate determinants could be intrinsically “tuned” to balance the frequency symmetrical duplicative and terminal divisions. Alternatively, fate balanced could be enforced through extrinsic factors where, for example, cell loss through differentiation promotes the symmetrical division of neighbouring cells, or *vice versa*. Crucially, in both cases, long-term, the clonal dynamics of tissue-maintaining cells converge towards a hallmark average clone size dependence and scaling size distributions predicted by the voter model (*30*, *31*).

By unhappy chance, in the two-dimensional geometry of epidermis, analytical studies show that the clone size distribution converges on a simple exponential size dependence for both intrinsically and extrinsically regulated fate behaviour. By contrast, the average clone size dependences are inequivalent, with intrinsically regulated stochastic fate translating to a linear growth characteristic, while extrinsic regulation leads to a *t/ln(t)* time dependence (*31*). However, with a cycle times of a week or more, logarithmic time dependences are hard to resolve of the lifetime of the mouse, and the nature of fate regulation –intrinsic vs. extrinsic- remains the subject of ongoing debate (*32–37*).

From these tracing studies, it follows that tissue-maintaining cells in epithelia are not individually long-lived; rather, long-term self-renewal potential is a property of the ensemble of basal progenitors that achieve homeostasis through stochastic loss and replacement. Indeed, the resolution of scaling behaviors in the clone size dependences provide evidence for stochastic stem cell self-renewal strategies in other tissues, include the mouse and drosophila germ line (*38–41*), intestine (*42*, *43*) and trachea (*44*). However, convergence to scaling behavior leads to partial erasure of lineage-specific information so that lineage tracing experiments do not inform on how stochastic fate behaviour is regulated at the molecular scale. In particular, scaling behaviour alone does not tell us whether the tissue-maintaining cells support a deeper hierarchy hosting progenitors with more limited proliferative potential; or whether the fate potential of stem cells is “reset” through each round of division, or whether cells transfer reversibly between states primed for renewal or differentiation (*45*).

Through advances in single-cell profiling, genome editing and lineage tracing our ability to probe and manipulate biological systems has never been greater. With the avalanche of molecular characterisations mounting, an increasing emphasis on descriptive methods based on correlative measures is threatening traditional hypothesis-driven approaches to studying higher level biological function (*46*). To truly profit from developments in quantitative biology, novel approaches must be developed that can integrate information across length scales, from molecules to cells and tissues. To meet this challenge, lessons and concepts from statistical physics are likely to play a crucial role. By tailoring questions to the right level of abstraction, we can gain predictive mechanistic insights into the behaviour of

complex biological processes. Central to this endeavour will be the identification of degrees of freedom that emerge from collective dynamics at the molecular or cellular scale.

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Special interest (•) or outstanding interest (••)

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Figure captions

Figure 1 Schematic showing the principle of renormalization group flow. Systems undergoing continuous phase transitions can be prepared in a state where statistical fluctuations become scale free. Systems far from thermal equilibrium, like biological systems, can approach such states through collective dynamics (gray line). Mathematically, critical systems form a subset (dotted area) of all possible systems described by a set of parameters p_1,p_2, … . Successive coarse graining (renormalization) drives a broad range of

critical systems into the same “hydrodynamic” attractor theory encapsulating the basic symmetries of the microscopic system.

Figure 2 Scaling clone dynamics in the mouse esophageal epithelium. (A) Schematic showing the organization of the stratified squamous epithelium in the mammalian interfollicular epidermis and esophagus. When basal cells commit to terminal differentiation, they detach from the basement membrane and move through the suprabasal layers eventually becoming shed at the surface. (B) Typical basal footprint of clones marked with a yellow fluorescent reporter gene at 3 days, 3 weeks, 3 month, and 12 months post-induction. (Scale bar=10 microns). (C) Schematic showing clonal dynamics in the basal cell layer. In homeostasis, proliferation within the basal layer (right) must be compensated by loss through differentiation (left) leading to clone expansion (blue) and contraction (red). When these events are correlated locally in space, clonal dynamics converges to the two-dimensional voter model universality class (see main text). When these events are uncorrelated, the clonal dynamics converges to the universality class of a critical birth-death process (equivalent to the infinite dimensional voter model). (D) Basal clone sizes recorded over the 1 year chase. Clonal loss (upper left panel) is compensated by a linear-like increase in the average clone size (middle panel) so that the total average clone size remains constant (upper right panel). (E) Cumulative clone size distribution shows convergence onto a scaling distribution in which the chance of finding a clone larger than some multiple of the average becomes constant over time, with an exponential size dependence. Panels C-E are reproduced with permission from Doupe et al. (2012).

Figure 1. Rulands and Simons

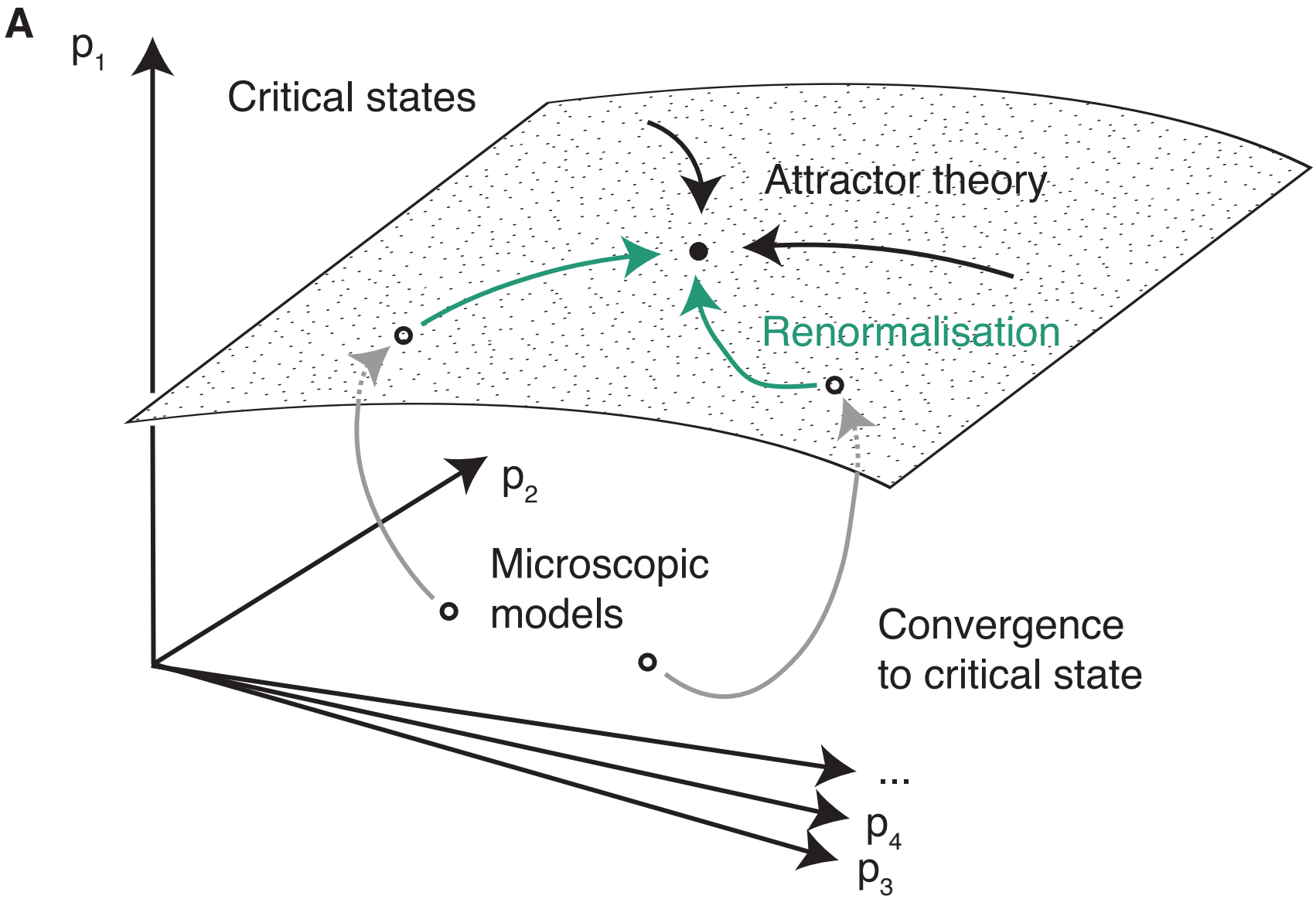

Figure 2. Rulands and Simons